Optimizing diagnostics for patient tailored treatment choices in patients with metastatic renal cell carcinoma and breast cancer

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General introduction and outline of the thesis

Providing personalized cancer treatment is an important aim in current cancer care. The ultimate goal is to choose the right treatment for the right patient at the right time. However, with an increasing number of new cancer drugs, there is an unmet need for predictive biomarkers to support proper decision making. Moreover, the selection of potential biomarkers is complicated by inter- and intratumor heterogeneity of tumor characteristics.

The aim of this thesis is to contribute to the development of biomarkers and optimal diagnostics with a focus on renal cell carcinoma (RCC) and breast cancer (BC). The main part of the thesis is centered around imaging and its potential role in decision making. Two chapters concentrate on diagnostics for bone metastases with imaging-based and pathology-based approaches in BC. In addition to tumor characteristics, which play a major role in personalized medicine, also patient characteristics are of importance. Therefore, in this thesis, one chapter is dedicated to the patient factor age.

The thesis consists of two parts. The first part comprises research in the field of RCC, the second part contributes to the BC field.

PART I

Clear cell RCC is characterized by Von Hippel-Lindau gene inactivation leading to the expression of proangiogenic growth factors such as vascular endothelial growth factor (VEGF-A) which results in typical vascular tumors. A high baseline plasma VEGF-A level is associated with shorter progression-free survival (PFS) and overall survival (OS) in metastatic RCC (mRCC) and is an independent prognostic factor [(1)]. The course of the disease varies tremendously among patients. Patients can have stable disease for years without any systemic therapy, while others present with rapidly progressive disease. Treatment options for metastatic disease consist of immune checkpoint inhibitors, angiogenesis inhibitors, and mammalian target of rapamycin (mTOR) inhibitors. In daily practice, it is difficult to predict the course of the disease. Consequently, it is difficult to decide whether watchful waiting or immediate initiation of systemic treatment is indicated for patients with metastatic disease. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET visualizes metabolic activity and high tumor ^{18}F-FDG uptake is associated with shorter OS in mRCC patients [(2)]. Carbonic anhydrase IX (CAIX) is a cell-surface expressed glycoprotein, which is overexpressed in RCC, while not present in healthy tissue. Girentuximab is an antibody against CAIX which, labeled to a radionuclide, can visualize CAIX expressing cells.

In **chapter 2** we evaluate the lesion detection of contrast-enhanced computed tomography (ceCT) scan, ^{18}F-FDG PET and ^{89}Zr-girentuximab PET in 42 patients with RCC with the first presentation of metastatic disease. Newly diagnosed patients with mRCC with good or

intermediate prognosis according to the International Metastatic RCC Database Consortium (IMDC) criteria [(3)], in whom watchful waiting was an option, were included in this study. Together with standard ceCT scan they underwent ^{18}F-FDG PET and ^{89}Zr-girentuximab PET at baseline before initiating watchful waiting. The CT scan was revised by two radiologists, ^{18}F-FDG PET was evaluated in detail by one nuclear physician and ^{89}Zr-girentuximab PET scan was evaluated by three or four nuclear medicine physicians. All tumor lesions were documented for the three modalities separately, while the evaluators were blinded for the other modalities. Lesion detection rates for the 3 modalities separated as well as for ^{18}F-FDG PET plus ceCT and ^{89}Zr-girentuximab PET plus ceCT were calculated. For lesions with ^{89}Zr-girentuximab or ^{18}F-FDG uptake visually exceeding background uptake, maximum standardized uptake values (SUV_{max}) were measured. We assessed biodistribution of ^{89}Zr-girentuximab as well as determinants for ^{18}F-FDG and ^{89}Zr-girentuximab tracer uptake.

Bevacizumab is a VEGF-A binding antibody that can be radiolabeled for imaging, but it is also an established first-line treatment option for patients with mRCC, in combination with interferon-α (IFN-α; immunotherapy). Another first-line treatment option is the tyrosine kinase inhibitor sunitinib which blocks VEGF receptors. mTOR plays a key role in cell growth, protein translation, autophagy, and metabolism. Blocking mTOR causes cell cycle arrest, but apart from a direct antitumor effect, mTOR inhibitors block VEGF-A expression and angiogenesis [(4)]. Everolimus is an mTOR inhibitor with antitumor activity in mRCC after progression on angiogenesis inhibitors. In chapter 3 we investigate the feasibility of serial ^{89}Zr-bevacizumab PET imaging in mRCC patients and we describe the change of ^{89}Zr-bevacizumab uptake in tumor lesions during treatment with either bevacizumab plus IFN-α or sunitinib. In chapter 4 we evaluate the change of tumor ^{89}Zr-bevacizumab uptake after the start of everolimus and explore whether ^{89}Zr-bevacizumab PET can identify patients with early disease progression.

In **chapter 3**, we describe a study on 22 patients with mRCC who underwent ^{89}Zr-bevacizumab PET scans at baseline and two and six weeks after initiating first-line non-curative antiangiogenic treatment, either bevacizumab plus IFN-α or sunitinib. The primary aim was to quantify ^{89}Zr-bevacizumab uptake in tumor lesions before treatment and changes in uptake during the early course of antiangiogenic therapy. Furthermore, we wanted to explore whether ^{89}Zr-bevacizumab PET can identify primary resistant disease early and whether tumor ^{89}Zr-bevacizumab uptake correlates with plasma VEGF-A, and the effect of two drug-free weeks after four weeks of sunitinib on tumor ^{89}Zr-bevacizumab uptake.

In **chapter 4**, we describe a study on patients with mRCC who underwent ^{89}Zr-bevacizumab PET scans prior to starting and after two and six weeks of everolimus treatment. Tumor tracer

uptake was quantified using SUVmax. The endpoints were change in tumor tracer uptake and treatment response on ceCT scan after three months. Furthermore, serum samples were collected before every tracer injection, at days -4, day 11 and day 39, for analysis of circulating VEGF-A levels, with day 0 being the day of baseline PET scan and the start of everolimus treatment to explore (change of) plasma VEGF-A levels during treatment and its correlation with (change of) SUVmax.

These first 3 chapters focus on molecular characteristics of clear cell RCC and their potential role as biomarkers that can guide personalized medicine. Besides tumor characteristics, also patient factors should be taken into account when aiming for personalized medicine.

The number of elderly patients with RCC is raising. There are important differences between elderly and younger individuals that can potentially affect tolerance of treatment [5]. However, elderly patients are underrepresented in clinical trials and rarely reported on separately.

In **chapter 5**, reports of phase III clinical trials and expanded access programs of approved drugs for mRCC are reviewed. Additionally, PubMed was searched for relevant articles and American Society of Clinical Oncology (ASCO) annual, ASCO Genitourinary and European Society for Medical Oncology (ESMO) 2014 and 2015 were searched for applicable presented abstracts. Additionally, National Comprehensive Cancer Network (NCCN), European Association of Urology (EAU) and ESMO guidelines were consulted. Available data is summarized for efficacy and toxicity in elderly patients and where possible we provided evidence-based recommendations for treatment choices in this population.

PART II

BC is the most common malignancy amongst women worldwide, with the second-highest rate of cancer-related deaths [6]. Besides the continuous development of new treatment strategies, there is an increasing effort to improve diagnostics as well. Worldwide, numerous PET tracers are being developed and tested. However, implementation is impaired by a slow collection of the required evidence to justify the implementation of these tracers in standard practice. It is of great importance to better define the value of already available diagnostics. Bone metastases are dominant in 70% of the patients with metastatic BC (mBC) [7] and often patients relapse with bone-only disease [8]. It is neither clear yet how to interpret immunohistochemical results for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) of decalcified bone metastases nor how to optimally visualize bone metastases, with either bone scan or ^{18}F-FDG PET.

In **chapter 6**, a systematic review enumerates all finished and ongoing research with respect

to (new) PET tracers evaluated in patients with BC. The aim of this review is to describe the process of the development of PET tracers and the level of evidence needed for their use in BC. We studied trials that have been performed with ^{18}F-FDG, 3'-deoxy-3-^{18}F-fluorothymidine and ^{18}F-fluoroestradiol to learn lessons for implementation of novel tracers. After defining the gap between a good rationale for a tracer and the implementation to the clinic, we propose solutions to fill the gap to try to bring more PET tracers to daily clinical practice.

Studies showed that ^{18}F-FDG PET has a higher sensitivity and specificity for identifying bone lesions in patients with breast cancer than Technetium-99m-diphosphonate (^{99m}Tc-DP) whole-body bone scintigraphy (BS) [9-13]. In **chapter 7** the influence of the detection discrepancies of bone lesions between BS and ^{18}F-FDG PET for management recommendations is evaluated in 102 women with first presentation of mBC. CeCT, BS and ^{18}F-FDG PET were performed within a 50 days' time frame. All three modalities were evaluated individually for bone lesions by expert physicians blinded for other imaging results. A multidisciplinary expert panel, consisting of at least two medical oncologists and one radiation oncologist, was asked to make management recommendations two times for each patient; once based on clinical information, ceCT and BS and once based on clinical information, ceCT scan and ^{18}F-FDG PET. The aim was to evaluate how often ^{18}F-FDG PET plus ceCT assessment of bone lesions leads to a clinically relevant change of management recommendations for patients with newly mBC, compared to BS plus ceCT. Clinically relevant management differences between the two recommendations were defined as 1) different treatment intent (curative, non-curative or unable to determine) and/or 2) different systemic or local treatment. Furthermore, we explored whether routine clinical characteristics could potentially predict (lack of) added ^{18}F-FDG PET value.

Chapter 8 describes the methods and accuracy of immunohistochemical staining for ER, PR and HER2 as well as fluorescence in situ hybridization of bone tissue in BC. According to guidelines, the first recurrence of BC should be biopsied for determination of ER/PR and HER2 expression at the metastatic site. Fifty-one percent of all patients relapse with bone only disease [8]. Bone biopsies must be decalcified before they can be sliced, stained and interpreted by the pathologist. It is not clear whether successful immunohistochemical staining is possible and whether obtained immunohistochemical results are reliable after the decalcification process. We aimed to determine the optimal decalcification method by subjecting residual fresh primary breast tumors to different decalcification methods and to study discordance of receptor expression between paired primary breast tumors and optimally decalcified bone metastases of 77 patients with newly mBC who participated in the IMPACT-MBC trial (NCT01957332).

Chapter 9 summarizes the thesis and in **chapter 10**, the new findings of this thesis and future perspectives are discussed. **Chapter 11** comprises a summary in Dutch.

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PART I